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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,028	03/14/2005	Christopher M. Starr	15021-6	1759

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
12/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,028	STARR ET AL.	
	Examiner	Art Unit	
	Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *6 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/25/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. Request for continued examination (i.e., RCE) under 37 C.F.R. §1.114, including the fee set forth in 37 C.F.R. §1.17(e), was filed in this application on 12 November 2009 after a Final action mailed 17 August 2009. Since this application is eligible for continued examination under 37 C.F.R. §1.114, and the fee set forth in 37 C.F.R. §1.17(e) has been timely paid, the finality of the previous Office action mailed 17 August 2009 has been withdrawn pursuant to 37 C.F.R. §1.114. Applicants' submissions filed 12 November 2009 have been entered. Accordingly an RCE has been established and the action on RCE follows.

Informal Matters

2. Applicants' Responsive amendment and responsc filed 12 November 2009 is acknowledged and entered.

3. Also acknowledged and entered is the Declaration under 37 C.F.R. §1.132 by Wilfred A. Jefferies.

4. The instant application contains claims 6 and 15 drawn to an invention not distinctly and specifically traversed in response filed 08 November 2007 to Election/Restriction requirement mailed 09 May 2007. A complete reply to the instant final rejection must include cancellation of nonelected claim or other appropriate action (See, 37 C.F.R. §1.144 and M.P.E.P. §821.01).

Claims Status

5. Claims 21-29 have currently been canceled.

6. Claims 6 and 15 have been withdrawn.

7. Claims 1-20 are currently pending.

8. Claims 1-5, 7-14 and 16-20 are currently under examination and are examined on merits.

Information Disclosure Statement

9. Information Disclosure Statement filed 25 November 2009 is acknowledged, has been made of record, considered and duly initialed PTO FORM 1449 is enclosed with the instant Office Action.

Claim Rejections - 35 U.S.C. §112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

11. Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled (See, e.g., Examples 1-5) for:

- localization of p97 in the lysosome of a cell;
- preparation of p97 linked to a fluorescent marker for its detection in a cell having lysosome;
- preparation of compositions comprising p97 linked to a protein for its administration to a patient;
- potential modes (i.e., oral or other) to administer said compositions to a patient in need thereof, i.e., suffering from a lysosomal disease; and
- evaluation methods to determine the efficacy of said administration in a patient;

is not, however, *enabled* for a method to treat a subject having a lysosomal storage disease, wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient.

In response filed 12 November 2009 to the above-recited rejection to Claims 1-5, 7-14 and 16-20 in the Office Action mailed 17 August 2009, the presented arguments are that "in-vitro data disclosed in this application are enabling, as the demonstration of in vitro p97 localization to the lysosome and characterization of p97-enzyme conjugates correlates with the in vivo effect." (See Remarks, Filed 12 November 2009, Page 6, Lines 28-32). Applicants further argue that in first Jefferies Declaration at paragraphs 8 and 9 demonstrate that the p97 is transcytosed across the blood brain barrier in a model known to correlate with blood brain barrier transcytosis in vivo; --- the data shows that the fusion of p97 with a lysosomal enzyme is enzymatically active, the structural integrity of said lysosomal enzyme is maintained and the p97 can be released inside the lysosome and therefore "data provides a clear

correlation to the in vivo delivery of enzyme via p97 to the lysosome of the cell" (See Remarks, Filed 12 November 2009, Page 6, Lines 39-41 and Page 6, Lines 4-9). Further referring to another declaration from Dr. Wilfred Jefferies, Applicants argue that Applicants have shown that another enzyme: N-acetylglucosaminisdase (NAGLU)-mediated experiments have also successfully shown results similar to those with iduronidase (See Remarks, Filed 12 November 2009, Page 7, Lines 27-32).

First of all, Applicants claim a method to treat a subject having a lysosomal storage disease by administering to said subject a composition comprising a p97 molecule covalently linked to a protein whose deficiency causes said disease. Applicants have elected β-hexosaminidase A to be said protein. Examiner reiterates, in the specification, and in the declarations from Dr. Jefferies filed 28 April 2009 and on 12 November 2009; the data presented is on the p97 covalently linked to enzymes other than the elected β-hexosaminidase A. Applicants' claimed invention comprising β-hexosaminidase A in the composition that is administered to the cell culture or the patient is not enabled because the currently presented specification demonstrates the claimed invention under *in vitro* conditions, which do not present the:

(i) Blood brain barrier, because the actual results from each of experiments 3 and 5 on the excretion of enzyme substrate in urine have not been presented in the currently described specification and is therefore, merely a contemplation, not a conducted experiment;

(ii) Applicants have presented in the specification data that the p97 covalently bound enzymes iduronidase are effective in a cellular lysosome, not in a cell having conditions similar to a brain cell having blood brain barrier and further stated that N-acetylglucosaminisdase has similar effect as iduronidase in the remarks filed 11/25/2009 (See Page 7, Lines 27-32) ;

(iii) Applicants themselves have presented a large number of references including some of the publications from Dr. Jefferies (see, e.g., the citation, "The blood/brain barrier prevents the passive diffusion of proteins" in NATURE VOL. 312, Page 162, 8 NOVEMBER 1984) through the IDS filed 11/15/2009, wherein the major hindrance to treat any lysosomal storage disease is because of the non-ability of a treatment composition to transfuse across the blood brain barrier;

(iv) According to Applicants' demonstrations and the declarations from Dr Jefferies on 28 April 2009 and on 25 November 2009, the p-97 and its conjugated partner have been targeted in to the

lysosome of a cell, but Applicants have yet experimentally not demonstrated, either in the specification of instant application; or in a pertinent art publication that said targeting is successful wherein the transcytosis has actually taken place in a lysosome of a cell faced with blood brain barrier wherein a composition comprising p97 conjugated to β-hexosaminidase A has been tested ;

(v) Additionally, the iduronidase and N-acetylglucosaminisdase that Applicants have demonstrated to be effective in the *in vitro* experiments as Applicants mention in the remarks filed on 12 November 2009 and in the Declarations from Dr. Jefferies on 28 April 2009 and on 25 November 2009 respectively, are entirely different enzymes than the Applicants' elected enzyme β-hexosaminidase A. This is because each of the three enzymes (i.e., iduronidase, N-acetylglucosaminisdase and β-hexosaminidase A) catalyze different reactions having different substrates and further different classification number (i.e., E.C. numbers) for said enzymes according to the "International Nomenclature Committee of enzymes (See attached Print outs from the IUBMB site). Therefore, even if Applicants' claimed invention is demonstrated to be successful with iduronidase and N-acetylglucosaminisdase as Applicants assert, it may not be successful with the elected enzyme β-hexosaminidase A; because, e.g., of the different enzyme-ligand interactions for each of the mentioned enzymes (See at the "BRENDA" site in attached Print outs from the IUBMB site); and

(vi) Applicants have admitted on record that the Applicants' claimed method is an "improvement" over the art-known prior method of enzyme therapy as the basis to treat lysosomal storage disease. Accordingly, the claimed invention is not enabled in absence of convincing data evidencing that the subjects administered with said composition (i.e., p97 covalently linked or fused to β-hexosaminidase) have been treated of the lysosomal storage disease. This is because the present data shows presence of iduronidase, or p97 in the lysosomal cell *in vitro*, not post administration of a composition comprising, e.g., p97 covalently linked or fused to β-hexosaminidase to a **subject** suffering from a lysosomal storage disease.

(vii) Furthermore in paragraph 11 of the Declaration from Dr. Jefferies filed 28 April 2009 and paragraphs 6-15 of the Declaration filed 25 November 2009, Dr. Jefferies has discussed fluorescently labeled iduronidase, or fluorescently-labeled p97, not the information on urine-excreted substrate of β-hexosaminidase according to the protocols in currently presented experiments 3 and/or 5. There is no linker or fusion protein in said preparations/compositions with β-hexosaminidase. Furthermore, mere presence of said enzyme (i.e., iduronidase) in the lysosome

of a cell *in vitro* does not convincingly give evidence that a subject administered a composition comprising iduronidase covalently linked to p97 has been treated with a lysosomal storage disease, especially in the absence of concrete evidence that: said composition is comprised of a linker as claimed instantly.

Applicants' arguments and the Declaration under 37 C.F. R. §1.132 from Dr. Jefferies filed 25 November 2009 regarding the lack of enablement rejection of Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §112, 1st Paragraph in the Office Action mailed 17 August 2009 have been fully and carefully considered but are not persuasive for the reasons of record at pages 4-6 in the Office Action mailed 17 August 2009 and those discussed *supra*. Thus, the rejection of Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §112, 1st Paragraph in the Office Action mailed 17 August 2009 is maintained and is adhered to.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. For the aforementioned reasons, no claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached at (571)-272-0939 Monday through Thursday 8:30 A.M. to 5:30 P.M. and on Fridays between 7.30 A.M. to 4.30 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Kailash C Srivastava/
Examiner, Art Unit 1657

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16 December 2009